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10/689,892	10/20/2003	N. Leigh Anderson	41119B	3893

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/689,892	ANDERSON, N. LEIGH	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 32-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-31* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants response filed September 7, 2007 is acknowledged

Status of the Claims

2. Claims 1-39 are currently pending

3. Applicant's response to the Restriction and/or Election of Species requirements is acknowledged (Applicant elected ***without traverse*** Group IV, claims 19-31) and claims 1-18 and 32-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see below i.e., ***Response to Restriction and/or Election of Species***).

4. Applicant's election of species is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

5. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

6. Therefore, claims 19-31 are examined on the merits in this action.

Information Disclosure Statement

7. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action (e.g., 5/16/05).

Specification

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Objections to the Claims

9. Claim 19 is objected to because of the following informalities:

A. This application contains "hybrid" claims that are based in part on a nonelected invention (e.g., claim 19 is "dependent" on non-elected claims 3 and 7). See MPEP § 821. The Examiner recommends amending claim 19 to incorporate the limitations of the non-elected subject matter.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 21-23, 24, 25, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 21**, the phrase "the method of claim 18" is vague and indefinite because

claim 18 does not describe a method but, rather, a non-elected microarray product. Therefore, claims 21 and all dependent claims (i.e., 22 and 23) are rejected under 35 U.S.C. 112, second paragraph.

B. **Claims 24 and 25** recite the limitation "the nucleic acid" in line 1. There is insufficient antecedent basis for this limitation in the claim. Therefore, claims 24, 25 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. **Claim 27** recites the limitation "the number of molecules of nucleic acid" in line 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 27 and all dependent claims are rejected under 35 USC 112, second paragraph.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 19-31 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

Applicant's claims are directed to a broad genus of methods for determining the presence of a ligand in a sample. The method employs the use of at least one recombinant microorganism

or a receptor and at least one ligand (e.g., see independent claim 19). Such claims represent broad scope because the nature of the microorganisms is not limited in any way (e.g., bacteriophage, yeast, animal cells, bacteria, etc. living in ocean, soil, air). For example, the San Diego Earth Times stated that the number of prokaryotes alone has been estimated at roughly five trillion trillion. That is, "If each bacterium were a penny, the stack would reach a trillion light years." (e.g., see San Diego Earth Times, First-ever estimate of total bacteria on search. Published on September 1997, retrieved from http://www.sdearthtimes.com/et0998s8.htm on October 28, 2007, pages 1; see also Whitman et al., "Prokaryotes: The unseen majority" *PNAS* **1998**, *95*, 6578-6583). In addition, the San Diego Earth Times notes that these microorganism are highly diverse located some 40 miles above the earth to deep below the ocean floor (e.g., see San Diego Earth Times, page 2) and that researchers have a tough time even trying to classify the myriad of species (e.g., see San Diego Earth Times, page 3). Furthermore, the number of atoms, types of atoms or manner in which said atoms are connected to form the receptor/ligand have not been specified. Thus, these terms also read on virtually an infinite number of possibilities. Furthermore, the dependent claims fail to limit one or more of these entities to anything less than virtually an infinite number of possibilities.

In contrast, Applicants disclose in the specification only one working example of an antibody phage library (e.g., see examples and figures; see also page 4, first full paragraph, "The present invention utilizes an antibody phage display library"; see also example 1 wherein the M13 phage is disclosed). In addition, a small "laundry list" of potential other microorganisms was also disclosed (e.g., see page 18, lines 14-17, "Other microorganisms or even cells may be used such as E. coli containing antibody or other receptor genes cloned in a plasmid, cosmid,

BAC or integrated into the genome, yeast particles containing a receptor or antibody gene a wide assortment of viruses and subcellular particles") but Applicants provide no guidance/working examples for these systems.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). Furthermore, a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because, as noted above, the variation within the currently claimed microorganisms, receptors and ligands would be almost incomprehensible (e.g., the number of microorganisms are so pervasive and diverse that they cannot even be completely classified). Thus, Applicants' one working example of an antibody phage display library does not suffice as a representative example.

Furthermore, the general knowledge and level of skill in the art do not supplement the omitted description because no known structure/function relationship and/or chemical properties exists that could otherwise be used to show possession of the enormous genus. In addition, there

is no known generally accepted method for producing the wide array of receptors/microorganisms used in the claimed methods. The genes of many microorganisms cannot be easily manipulated for expression of a specific receptor. For example, Heuer et al. state:

> In molecular biology, the genetic manipulation of organisms resulting in the inactivation of a special gene of interest or the expression of fusion proteins represents he gold standard to characterize the function and localization of a protein. Despite the fact that diverse methods have been established for introducing and stably integrating heterologous DNA in the genomes of many bacteria, such techniques and therefore the possibility to genetically manipulate are missing for chlamydial species. This genetic intractability of Chlamydia is the main obstacle against their efficient molecular investigation. Reasons that are likely to account for the chlamydial inaccessibility are manifold, and barriers for DNA transformation may exist at several distinct levels, including (i) DNA uptake, (ii) stable DNA integration and (iii) clonal bacterial propagation and selection.

(Huer et al. "Tackling the intractable – Approaching the genetics of Chlamydiales" International Journal of Medical Microbiology 2007, 297, 569-676, page 570, column 2, first full paragraph; see also abstract, "Despite intense research on Chlamydiaceae ... genetic manipulation still remains impossible"). In addition, many of the microorganisms that could be easily manipulated to express a receptor on their surfaces cannot be stably cultured for manipulation in a screening method. For example, Thompson-Chagoyan et al. state, "intestinal bacteria that live in an anaerobic environment are difficult or impossible to culture outside the intestine" (e.g., see Thompson-chagoyan et al., "Colonization and impact of disease and other factors on intestinal microbiota." Digestive diseases and sciences, (2007 Sep) Vol. 52, No. 9, pp. 2069-77"). This is because many of the bacteria are "symbiotic" and cannot live apart from their natural environments (e.g., see Muller et al., "Sustainable Production of Bioactive Compounds by Sponges – Cell Culture and Gene Cluster Approach: A Review" Marine Biotechnology 2004, 6, 105-117, especially abstract, "the predominant number of 'symbiotic bacteria' proved to be nonculturable") or have specialized nutrient requirements that cannot be easily provided or

required (e.g., see Siqueira et al. "PCR methodology as a valuable tool for identification of endodontic pathogens" *Journal of Dentistry 2003, 31,* 333-339 wherein various "fastidious" pathogens are disclosed that are also impossible to culture).

Furthermore, not all receptor are compatible with this diverse range of microorganisms. For example, the expression of eukaryotic receptors would be problematic according to Seed and Smith (e.g., see Seed, B. "Developments in expression cloning" Current Opinion in Biotechnology 1995, 6, 567-573, especially page 567, column 2, second paragraph, "The second obstacle to expression of eukaryotic genes in prokaryotes is the foreign environment of the bacterial cytosol. This substantially reduces the fraction of polypeptides that will properly fold to adopt a native configuration"; see also Smith, G.P. Science, 1985, 228, 1315-1317, outlining problems with phage display e.g., "The phage-display method ... at present has problems such as ... proteins harmful to *E. coli*, proteins degraded in *E. coli* and proteins which cannot permeate membranes of *E. coli* cannot be displayed"). Thus, even though a specific receptor can be expressed it will not adopt the proper folding.

Thus, the claims fail to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result (i.e., the use of "all" microorganisms, receptors, ligands), far beyond those means actually discovered or contemplated by the inventor (i.e. antibody phage display), so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119. In sum, it would take trillions of years to adequately characterize the

estimated five trillion trillion microorganisms and the virtually unlimited number of microorganism/receptor combinations that would stem therefrom. Furthermore, the vast majority of these microorganisms cannot be isolated, cultured, or genetically manipulated sufficiently to participate in the claimed method (see above). Thus, Applicants were not in possession of the "full scope" of the claimed invention.

12. Claims 19-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for phage display of antibodies, does not reasonably provide enablement for the use of an microorganism displaying any receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Applicant's claims are directed to a broad genus of methods for determining the presence of a ligand in a sample. The method employs the use of at least one recombinant microorganism or a receptor and at least one ligand (e.g., see independent claim 19). Such claims represent broad scope because the nature of the microorganism is not limited including its habitat (e.g., ocean, soil, air), genetic constitution (e.g., bacteriophage, yeast, animal cells, bacteria, etc.), etc. For example, the San Diego Earth Times stated that the number of prokaryotes alone has been estimated at roughly five trillion trillion. That is, "If each bacterium were a penny, the stack would reach a trillion light years." (e.g., see San Diego Earth Times, First-ever estimate of total bacteria on search. Published on September 1997, retrieved from http://www.sdearthtimes.com/et0998s8.htm on October 28, 2007, pages 1; see also Whitman et al., "Prokaryotes: The unseen majority" *PNAS* **1998**, *95*, 6578-6583). In addition, the San Diego Earth Times notes that these microorganism are highly diverse located some 40 miles above the earth to deep below the ocean floor (e.g., see San Diego Earth Times, page 2) and that researchers have a tough time even trying to classify the myriad of species (e.g., see San Diego Earth Times, page 3). Furthermore, the number of atoms, types of atoms or manner in which said atoms are connected to form the receptor/ligand have not been specified. Thus, these terms also read on virtually an infinite number of possibilities. Furthermore, the dependent claims fail to limit one or more of these entities to anything less than virtually an infinite number of possibilities. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Furthermore, the general knowledge and level of skill in the art do not supplement the omitted description

because no known structure/function relationship and/or chemical properties exists that could otherwise be used to show possession of the enormous genus. In addition, there is no known generally accepted method for producing the wide array of receptors/microorganisms used in the claimed methods. The genes of many microorganisms cannot be easily manipulated for expression of a specific receptor. For example, Heuer et al. state:

> In molecular biology, the genetic manipulation of organisms resulting in the inactivation of a special gene of interest or the expression of fusion proteins represents he gold standard to characterize the function and localization of a protein. Despite the fact that diverse methods have been established for introducing and stably integrating heterologous DNA in the genomes of many bacteria, such techniques and therefore the possibility to genetically manipulate are missing for chlamydial species. This genetic intractability of Chlamydia is the main obstacle against their efficient molecular investigation. Reasons that are likely to account for the chlamydial inaccessibility are manifold, and barriers for DNA transformation may exist at several distinct levels, including (i) DNA uptake, (ii) stable DNA integration and (iii) clonal bacterial propagation and selection.

(Huer et al. "Tackling the intractable – Approaching the genetics of Chlamydiales" International Journal of Medical Microbiology 2007, 297, 569-676, page 570, column 2, first full paragraph; see also abstract, "Despite intense research on Chlamydiaceae ... genetic manipulation still remains impossible"). In addition, many of the microorganisms used in the claimed method cannot even be stably cultured for genetic manipulation. For example, Thompson-Chagoyan et al. state, "intestinal bacteria that live in an anaerobic environment are difficult or impossible to culture outside the intestine" (e.g., see Thompson-chagoyan et al., "Colonization and impact of disease and other factors on intestinal microbiota." Digestive diseases and sciences, (2007 Sep) Vol. 52, No. 9, pp. 2069-77"). This is because many of the bacteria are "symbiotic" and cannot live apart from their natural environments (e.g., see Muller et al., "Sustainable Production of Bioactive Compounds by Sponges – Cell Culture and Gene Cluster Approach: A Review" Marine Biotechnology 2004, 6, 105-117, especially abstract, "the predominant number of 'symbiotic bacteria' proved to be nonculturable") or have specialized nutrient requirements that

cannot be easily provided or required (e.g., see Siqueira et al. "PCR methodology as a valuable tool for identification of endodontic pathogens" *Journal of Dentistry 2003, 31*, 333-339 wherein various "fastidious" pathogens are disclosed that are also impossible to culture).

Furthermore, not all receptor are compatible with this diverse range of microorganisms. For example, the expression of eukaryotic receptors would be problematic according to Seed and Smith (e.g., see Seed, B. "Developments in expression cloning" Current Opinion in Biotechnology 1995, 6, 567-573, especially page 567, column 2, second paragraph, "The second obstacle to expression of eukaryotic genes in prokaryotes is the foreign environment of the bacterial cytosol. This substantially reduces the fraction of polypeptides that will properly fold to adopt a native configuration"; see also Smith, G.P. Science, 1985, 228, 1315-1317, outlining problems with phage display e.g., "The phage-display method ... at present has problems such as ... proteins harmful to *E. coli*, proteins degraded in *E. coli* and proteins which cannot permeate membranes of *E. coli* cannot be displayed").

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have provided a single working example of a phage display library using M13 phage (e.g., see Example 1; see also figures).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must

be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991).

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 19-27 and 29-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Ruoslahti et al. (U.S. Pat. No. 6,303,573 B1) (Filing Date is **June 7, 1999**; Date of Patent is **October 16, 2001**) (5/16/05 IDS).

For ***claim 19***, Ruoslahti et al. disclose a method for identifying "homing" peptide "receptors" from a library of peptides via biopanning phage display techniques wherein said peptide "receptors" are expressed on the surface of a phage (i.e., recombinant microorganism) and bind to [and hence determine the presence of] heart and ischemic heart tissue "ligands" (see Ruoslahti et al., entire document, especially columns 21-24, examples 1-2), which anticipates the claimed invention. For example, Ruoslahti et al. disclose contacting phage peptide libraries with ligands from normal heart and ischemic heart, which reads on the first method step of claim 19 because the phage peptide

libraries represent "at least one recombinant microorganism" and these phage particles were placed in contact under binding conditions with ligands from heart and ischemic heart tissues (see Ruoslahti et al., column 21, Example 1, paragraphs 1-3; see also column 22, example II, paragraphs I and II). Ruoslahti et al. also disclose "rescuing" the recombinant phage for "second" and "third" rounds of selection before final purification of said phage (see Ruoslahti et al., column 21, example 1, last paragraph), which reads on the second step of claim 19 because the phage that bound to said heart or ischemic heart ligands were enhanced and purified relative to the phage that contained peptides that did not bind. Finally, Ruoslahti et al. also disclose taking "single stranded phage DNA from individual third round clones" and sequencing said DNA (see Ruoslahti et al., column 21, example 1 last paragraph), which reads on the last step in claim 19 because the nucleic acid that encodes the unique peptide that binds to the heart or ischemic heart ligands was enhanced via PCR and sequenced, which provided the identity of the binding peptide "receptors" (see Ruoslahti et al., column 10, lines 32-42, "Upon homing to cardiac tissue or ischemic tissue, the homing peptide can be identified by determining the sequence of the unique oligonucleotide tag using, or example, PCR ... Similarly, the nucleic acid sequence encoding a peptide displayed on a phage is another example of a specific nucleic acid tag, since sequencing of the nucleic acid identifies the amino acid sequence of the expressed peptide"; see also Ruoslahti et al., column 8, second to last paragraph, "[i]f desired, the peptides constituting the library can be linked to a common or unique tag, which can facilitate recovery and/or identification of the homing peptide"; see also Ruoslahti et al., column 9, last paragraph "A tag can be a shared tag ... to identify the

presence of a peptide of the library in a sample or to substantially isolate the homing peptides from a sample following in vivo panning. A shared tag such as biotin, for example, can be used to isolate a linked peptide from cardiac tissue or ischemic tissue using streptavidin affinity chromatorgraphy").

For ***claim 20***, Ruoslahti et al. disclose "quantitatively" determining the amount of phage that binds to ligands in heart and brain tissue and consequently the amount of sequence tag, which is contained within said phage (see Ruoslahti et al., figures 1-3, see also columns 21-24, examples 1-2).

For ***claim 21***, Ruoslahti et al. disclose the use of a "library" of peptides wherein some of the library members bind preferentially to ischemic heart tissue ligands and some of the library member bind preferentially to both heart and ischemic heart tissue ligands (see Ruoslahti et al., examples 1 and 2, see especially column 24, lines 35-40, "These results indicate that a heart homing peptide such as SEQ ID NO: 10 can selectively home to ischemic heart tissue without homing to normal tissue and can confer selective homing on a linked moiety such as a phage. These results further indicate that a heart homing peptide such as SEQ ID NO: 9 can target both ischemic and normal heart tissue"). Please note that claim 21 has been interpreted for the sake of compact prosecution as being dependent on claim 19 (see 2nd paragraph rejection above, denoted "A").

For ***claim 22***, Ruoslahti et al. disclose *in vivo* panning wherein said phages are exposed to many different ligands at widely different concentrations (see Ruoslahti et al., column 21-24, examples 1-2). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of

showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For ***claim 23***, Ruoslahti et al. disclose *in vivo* panning wherein said phages are used to detect the presence and hence "quantity" of ligands expressed on ischemic heart tissue (see Ruoslahti et al., column 21-24, examples 1-2).

For ***claim 24***, Ruoslahti et al. disclose labeling the nucleic acid containing the sequence tag with biotin (see Ruoslahti et al., column 10, last two paragraphs).

For ***claim 25***, Ruoslahti et al. disclose a "shared" nucleic acid tag that can be used to isolate peptides of a library from a sample (see Ruoslahti et al., column 10, second paragraph, especially lines 15-18, "An affinity column containing a nucleotide sequence that is complementary to the shared tag then can be used to isolate the homing peptides from an organ or tissue sample by hybridizing to the shared tag linked to the molecules").

For ***claim 26***, Ruoslahti et al. disclose that "an affinity column containing a nucleotide sequence that is complementary to the shared tag then can be used to isolate the homing peptides from an organ or tissue sample by hybridizing to the shared tag" (see Ruoslahti et al., column 10, second paragraph).

For ***claim 27***, Ruoslahti et al. disclose the use of PCR to amplify the nucleic acid sequence tag (see Ruoslahti et al., columns 21-24, examples 1-2, especially column 21, lines 40-41).

For ***claim 29***, Ruoslahti et al. disclose biopanning via phage display (see Ruoslahti et al., columns 21-24, examples 1-2, see especially column 21, lines 40-45, "Oligonucleotides were ... purified and ligated to the nucleic acid encoding the gene III protein in the Fuse5 vector such that, upon expression, the peptide is present as a fusion protein at the N-terminus of the gene III protein).

For ***claim 30***, Ruoslahti et al. disclose the use of PCR to amplify the nucleic acid sequence tag (see Ruoslahti et al., columns 21-24, examples 1-2, especially column 21, lines 40-41), which anticipates claim 30 (see also Ruoslahti et al., column 11, lines 5-8, "The isolated homing peptides can then be identified, for example, by PCR based DNA sequencing of the specific tag using the shared 3' nucleotide sequence of the nucleotide tag as a primer binding site").

For ***claim 31***, Ruoslahti et al. disclose determining calculating the amount of phage and consequently receptor and sequence tag contained therein relative to phage that binds to a brain "control" ligand (see Ruoslahti et al., column 24, lines 28-32).

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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